## Title

All-cause and cause-specific mortality in individuals with zero and minimal coronary artery calcium: A long-term, competing risk analysis in the Coronary Artery Calcium Consortium.



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**TITLE PAGE**

**Title:** All-Cause and Cause-Specific Mortality in Individuals with Zero and Minimal Coronary Artery Calcium: A Long-Term, Competing Risk Analysis in the Coronary Artery Calcium Consortium

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**Running Head:** Mortality in Zero and Minimal Coronary Calcification

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**ABSTRACT**

**Background**—There is increasing interest in zero coronary artery calcium (CAC) as a marker of sustained good health. The long-term associations between zero and minimal CAC and cause-specific mortality are currently unknown, particularly after accounting for competing risks with other causes of death.

**Methods and Results**—We evaluated 66,363 apparently healthy individuals from the CAC Consortium multi-center, observational, retrospective cohort study. Cohort entry expanded through 1991–2010 and follow-up information was obtained through 2014. All patients had CAC measured at baseline for clinical risk assessment, and were followed over mean 12 years for all-cause and cause-specific mortality, including coronary heart disease (CHD), cardiovascular disease (CVD) and cancer death. Patients with CAC=0 (45% prevalence) had stably low rates of CHD death, CVD death (ranging 0.32 to 0.43 per 1,000 person-years), and of all-cause death. Cancer was the predominant cause of death in this group ranging 0.47 to 0.79 per 1,000 person-years. Patients with CAC 1-10 had greater crude incidence of deaths from CHD and CVD, although multivariable-adjusted Fine and Gray competing risk regression models demonstrated a persistent relationship with CVD mortality (as compared to CAC=0) only under age 40. Patients with CAC>10 had multivariable-adjusted increased risks of CHD, CVD and all-cause mortality, and a greater proportion of deaths due to CVD.

**Conclusions**—Zero CAC, which is a frequent finding in patients undergoing clinical CAC scanning in the US, is associated with stably low rates of CVD mortality over 12-year follow-up. In this group of healthy agers, cancer is the predominant cause among the infrequent deaths. Our results support the emerging consensus that CAC=0 represents a unique population with highly favorable all-cause prognosis, who may be considered for more flexible treatment goals in primary prevention.

## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ACC/AHA | American College of Cardiology / American Heart Association |
| CAC | coronary artery calcium |
| CHD | coronary heart disease |
| CI | confidence interval |
| CT | computed tomography |
| CVD | cardiovascular disease |
| ICD | International Classification of Diseases |
| MESA | Multi-Ethnic Study of Atherosclerosis |
| SD | standard deviation |
| SHR | subdistribution hazard ratios |

## TEXT

## Introduction

There is increasing interest in zero coronary artery calcium (CAC) as a marker of sustained good health.[1,2] Prior studies have suggested very low 10-year rates of coronary heart disease (CHD) events, cardiovascular disease (CVD) events, and all-cause mortality in the presence of a CAC score of zero (CAC=0).[3–12] Indeed, CAC=0 appears to be the single strongest "negative risk factor" for incident CVD.[13] Consistent with this, recent guidelines from the American College of Cardiology and the American Heart Association (ACC/AHA) have assigned CAC a preeminent role in CVD risk assessment and endorse CAC=0 as a powerful marker of decreased CVD risk.[14]

Intriguingly, recent reports have also linked the absence of CAC with low rates of cancer and other non-CVD events such as incident chronic obstructive lung disease, chronic kidney disease, hip fracture, and dementia.[15] This has led to the hypothesis that the absence of CAC may be a marker of healthy "biologic aging". Supporting this view, even *minimal* CAC (Agatston scores of 1–10 units) have been associated with higher CVD events and all-cause mortality.[9,10]

However, there is little data available on the long-term associations of CAC=0, CAC 1-10, and higher CAC particularly after accounting for competing risks of cause-specific mortality. Currently, the predominant cause of infrequent death in those with CAC=0 is unknown, and the impact

of increasing CAC scores on CVD versus non-CVD causes of death remains unclear, as well as the potential impact of age and sex on these relationships.

Given the complicated association of CAC with risk of multiple diseases, we sought to conduct a competing risk analysis studying zero and minimal CAC within the CAC Consortium, a large cohort with long-term follow-up for cause-specific death.[16] Such data may be important for estimating prognosis and informing preventive strategies in patients at the low end of the risk spectrum.

## Methods

### *The CAC Consortium*

The characteristics of the CAC Consortium have been described elsewhere.[16–18] Briefly, this is a multi-center, retrospective cohort study of 66,636 consecutive patients undergoing routine clinical CAC scoring for CVD risk assessment in 4 high volume US centers. Patients were free of overt CVD or of clinically important CVD symptoms (i.e. typical angina or angina-equivalent) at cohort entry, which was defined by the time of the baseline CAC examination. Baseline data – including demographic characteristics, cardiovascular risk factors, and baseline CAC scores – was obtained at cohort entry through 1991 – 2010, and follow-up information was obtained through June 2014.

Prior analyses have shown that the baseline characteristics of the CAC Consortium population are similar to those of well-characterized, contemporary US cohorts such as NHANES 2001-2002, Framingham Offspring, and others.[16]

*Research Ethics*

Written informed consent for participation in research was collected at all centers prior to the baseline CAC scanning. Institutional review board approval for coordinating center activities including death ascertainment and death certificate collection was obtained at the Johns Hopkins Hospital (Baltimore, Maryland, USA).

*Study Population*

For the present analysis, all 66,363 patients from the CAC Consortium were included. Participants were categorized into three groups: CAC=0, minimal CAC (1-10), and CAC>0.

*Baseline Evaluation*

As described above, all patients in the CAC Consortium underwent a baseline computed tomographic (CT) scan. This included both patients scanned using electron beam tomography (93%), as well as in later years, patients scanned using multi-detector CT (7%). A common standard non-contrast cardiac-gated CT scanning protocol was used across sites, adapted to each CT scanner technology. CAC was scored using the Agatston method.[19]

In each center, data on self-reported cardiovascular risk factors, treatment use, and laboratory test results was collected as part of the routine clinical visit associated with the referral for CAC testing and/or from a semi-structured in-person interview. Details on the definitions used in the CAC Consortium for each cardiovascular risk factor have been described elsewhere,[16-18] and are summarized in the **Supplementary Methods** section of the online Supplementary Appendix. For each participant, 10-year atherosclerotic CVD risk was estimated using the Pooled Cohort Equations following current ACC/AHA guideline recommendations.[14]

*Event Definitions and Ascertainment*

The 4 primary outcomes for the present study were all-cause, CHD, CVD and cancer mortality, all assessed over mean 12 years follow-up (standard deviation [SD] 4 years, maximum follow-up across the 4 sites ranging from 13.6 to 22.5 years). Secondary study outcomes included stroke mortality, heart failure mortality, other circulatory disorder mortality (non-CHD, non-stroke), total non-CVD mortality (death from all causes except for CVD), and pulmonary mortality.

In the CAC Consortium, mortality was assessed via linkage of patient records with the Social Security Administration Death Master File using a previously validated algorithm. Death certificates were obtained from the National Death Index, and the underlying cause of death was categorized into common causes of death using the International Classification of

Diseases version 9 (ICD-9) and version 10 (ICD-10) codes as previously described.

*Statistical Analyses*

Baseline characteristics of the study participants were described overall and by three baseline CAC strata: CAC=0, CAC 1-10, and CAC>10. Number and proportion were used to summarize categorical variables, and mean ± SD or median and interquartile range were used for continuous variables depending on the normality of the data. Chi-square, ANOVA and Kruskal-Wallis tests were used for statistical comparisons across CAC groups as appropriate.

The cumulative incidence (incidence proportion, expressed in %) of all-cause and cause-specific death was calculated both overall as well as by baseline CAC burden. The proportion of deaths due to specific causes was also computed for each CAC strata, by dividing the number of cause-specific deaths by the total number of deaths observed in each group. All-cause and cause-specific incident mortality rates during follow-up were also calculated and expressed per 1,000 patient-years. These results were displayed graphically for assessment of trends over the course of follow-up.

Multivariable Cox proportional hazards regression models were used to assess the multivariable-adjusted associations between increasing baseline CAC burden (CAC 1-10 and CAC>10, respectively, compared to CAC=0) and all-cause mortality. In addition, for cause-specific death endpoints, competing risks regression using Fine and Gray models[20] were used to

examine the associations between CAC and CHD death, CVD death, and cancer death, respectively, accounting for competing risks with other causes of death. Results for the competing risks regression analyses are presented using subdistribution hazard ratios (SHR) with 95% confidence intervals (CI).

For all regression analyses, three hierarchical multivariable models were built with increasing levels of adjustment. Model 1 was unadjusted, Model 2 adjusted for age and sex, and Model 3 further adjusted for hypertension, current smoking, diabetes, dyslipidemia, and family history of CHD. In a sensitivity analysis we further adjusted for race/ethnicity, which was known for only 65% of the study participants included in the CAC Consortium.

Subgroup analyses were also conducted, stratifying by sex and age strata. Finally, exploratory analyses were also conducted, assessing the multivariable-adjusted associations between CAC categories and other relevant causes of death: stroke death, heart failure death, other circulatory disease death, any non-CVD death, and pulmonary death.

All analyses were conducted using Stata version 15.[21] A threshold of $p<0.05$ was used to define statistical significance.

## Results

### *Baseline Characteristics*

The mean age of the 66,363 patients included in the study was 54.5 years (SD 10.6), 33% were women, and the vast majority (89.1%) were non-

Hispanic Whites (**Table 1**). Dyslipidemia was the most prevalent cardiovascular risk factor (56.8%), while diabetes was the least (6.8%). The median estimated 10-year ASCVD risk was 4.4% (interquartile range 1.9 – 9.2).

At study baseline 29,575 (44.7%) patients had CAC=0, 7,808 (11.7%) had CAC 1-10, and 29,071 (43.6%) had CAC>10. Patients with higher CAC scores were significantly older, more likely to be male, had a greater burden of traditional CVD risk factors, and had a higher average 10-year estimated ASCVD risk.

*Incident Death Events during Follow-Up*

Over a 12-year mean follow-up, 3,158 deaths occurred, including 524 CHD deaths, 971 CVD deaths, and 1,129 cancer deaths. The lowest all-cause and cause-specific mortality risks were observed in patients with CAC=0 (0.17% for CHD mortality, 0.41% for CVD mortality, and 0.97% for cancer mortality) (**Figure 1**). Risks of death were slightly higher for patients in the CAC 1-10 group, and substantially higher for those with CAC>10.

*Cause of Death*

Cancer death was more frequent than CVD death in both CAC=0 and CAC 1-10 patients, while the opposite was true for CAC>10 patients (**Figure 1**). Specifically, among the 595 deaths occurring in the CAC=0 group, the predominant cause of death was cancer (288, 48% of total), while only 51 (9%) and 121 (20%) of deaths were due to CHD and CVD, respectively (**Figure 2, Panel A**). The proportion of deaths due to CHD and CVD both

increased with increasing CAC scores, while the proportion of cancer deaths decreased (**Figure 2, Panels B** and **C**).

*Trends in All-Cause and Cause-Specific Death Rates over Time*

In patients with CAC=0, cumulative incidence rates of all-cause death were stably low over time and were the lowest across all study groups, ranging 1.38 to 1.62 per 1,000 person-years (**Figure 3 Panel A**). Event rates were slightly higher in patients with CAC 1-10 (**Panel B**), although the highest rates were observed in patients with CAC >10—approximately 4-fold higher than those of CAC=0 patients.

**Figure 4** displays the cumulative incidence rates of CVD death and cancer death. In both patients with CAC=0 and CAC>0, there was a progressive decline in the cumulative rates of CVD death over time, the larger absolute decreases observed in patients CAC>0 and the largest relative decreases in those with CAC=0. In parallel, there was a progressive increase in the incidence of cancer death rates in both study groups. Specifically, in patients with CAC=0, at the end of follow-up cancer death rates were roughly 2.4-fold those for CVD death.

*Associations between Baseline CAC Burden, All-Cause and Cause-Specific Mortality*

In unadjusted analyses, compared to patients with CAC=0, those with CAC 1-10 had a 1.4-fold increased risk of death from any cause during follow-up, while those with CAC>10 had a 4-fold increased risk (**Table 2**). After adjusting for traditional risk factors, there was no longer an independent

association between CAC 1-10 and all-cause death, while patients with CAC>10 still had a 1.6-fold multivariable-adjusted increased risk of all-cause death compared to those with CAC=0.

In competing risk analyses, there were strong multivariable-adjusted associations between CAC>10 (as compared to CAC=0) with both CVD death (SHR 2.31, 95% CI 1.88, 2.85) and CHD death (SHR 2.31, 95% CI 1.88, 2.85). On the other hand, the association between CAC>10 and cancer death was much weaker (SHR 1.19, 95% CI 1.02, 1.40). For CAC 1-10, all 95% CIs included 1.00.

In sensitivity analyses within the subgroup with available race/ethnicity data, further adjustment for race/ethnicity did not significantly alter the results (data not shown).

*Subgroup Analyses*

Generally similar results were observed in analyses stratified by sex (**Table 3**). Nonetheless, the multivariable-adjusted associations between CAC>10 (as compared to CAC=0) and all-cause death, CVD death, and cancer death were all numerically stronger in women, while the association with CHD death was stronger in men.

In analyses stratified by age, the strongest associations between CAC>10 (as compared to CAC=0), all-cause death, CVD death, and cancer death were observed in the <40 years age stratum (**Table 4**). Very strong associations were also observed between CAC 1 – 10 (as compared to CAC=0), all-cause and CVD death in individuals <40 years. Conversely,

associations tended to be progressively weaker in age strata defined by increasing age.

*Exploratory Analyses*

**Supplementary Table S1** shows the results of competing risk multivariable regression analyses for other pertinent outcomes. Compared to CAC=0, CAC>10 was associated with a significantly greater risk of all causes of death evaluated including stroke, heart failure, other circulatory disease, total non-CVD death, and pulmonary death. Very strong multi-variable adjusted associations were also observed between CAC 1-10 (as compared to CAC=0), heart failure death and pulmonary death, although for the former outcome the 95% CIs were wide.

## Discussion

In the first large competing risks analysis of zero and *minimal* CAC and long-term cause-specific death, including 66,363 apparently healthy individuals undergoing clinical CAC scanning, we demonstrated that patients with CAC=0 (representing 45% of the study population) had stably low rates of CHD death, CVD death and all-cause death over 12-year follow-up. Cancer was the predominant cause of death in this group of healthy agers. While patients with CAC 1-10 had a greater crude incidence of deaths from CHD and CVD, multivariable-adjusted competing risk models demonstrated a persistent relationship with increased CVD mortality (as compared to CAC=0) only in patients <40 years old. Participants with CAC>10 had multivariable-

adjusted increased risks of CHD, CVD and all-cause mortality compared to those with CAC=0, with a greater proportion of deaths due to CVD vs. non-CVD causes in these individuals. These findings have implications for the allocation of preventive resources, particularly in patients at the low end of the risk spectrum.

Our results extend the work of prior studies examining the association of zero CAC, minimal (i.e., 1 – 10) CAC, and all-cause mortality. Our group previously demonstrated a very low death rate of approximately 0.5% over 5 years in a subset of CAC Consortium patients with CAC=0.[3] More recently, Valenti et al also found a very low mortality rate in asymptomatic patients with CAC=0 undergoing CAC scoring in a single Tennessee center extending to 15-year follow-up.[4] However, these two prior studies were limited by use of all-cause mortality as the only study outcome. Our present analysis adds to the existing literature by showing that in CAC=0 patients undergoing clinical CAC scanning for risk assessment purposes, death from any cause is a rare event at 12 years of follow-up, that CHD and CVD deaths are both very infrequent, and that cancer is the leading cause of death in this overall healthy group.

Our observations are also consistent with prior work showing low risk of CHD and CVD events in patients with CAC=0. For example, Budoff et al observed very low risk of CHD events amongst MESA participants from the Multi-Ethnic Study of Atherosclerosis (MESA), with 3-fold higher event rates in those with minimal CAC 1-10.[9] Silverman et al. demonstrated very low

rates of percutaneous coronary intervention and coronary artery bypass surgery over 8.5 years of follow-up amongst individuals with CAC=0 in MESA.[11] Expanding on non-CHD CVD endpoints, Gibson et al previously also demonstrated a low risk of stroke in MESA participants with zero CAC.[12]

The present results provide further support to recent US clinical practice guideline recommendations, which in recent years have given increasing recognition to the "power of zero".[22] This includes the 2017 guidelines from the Society of Cardiovascular Computed Tomography,[23] which articulated CAC=0 as a clinically actionable result, driving an enhanced clinician-patient risk discussion, with potential for selecting more flexible preventive treatment goals amongst these very low risk patients. Subsequently, the 2018 and 2019 ACC/AHA cardiovascular prevention guidelines brought CAC=0 to the forefront as a highly valuable tool for 'de-risking' patients who would otherwise be considered candidates for chronic statin therapy.[14,24] The fact that in our cohort almost half of the participants had a CAC score of zero (which is consistent with reports from other cohorts[3-10,25]) supports the potential value of actively screening for CAC=0, at least in a broad intermediate risk group.

Although cancer was the predominant cause of death in patients with CAC=0, death from cancer and from any other cause was a rare event during 12 years of follow-up in this healthy subgroup. Ours is not the first study to describe the low risk of non-CVD in patients with zero CAC. Indeed, Handy et al reported low rates of incident cancer, chronic kidney disease, chronic

obstructive pulmonary disease, hip fracture, and dementia-related hospitalizations in MESA.[15] This is consistent with the understanding that CAC serves as integrator of not only most upstream risk exposures, but also of individual vulnerability to their effects. Patients with CAC=0 and particularly those with CAC=0 over time[26,27] represent a unique group of overall "healthy agers" deserving further study.

A CAC score of 1-10 (as compared to CAC=0) was associated with a multivariable-adjusted increased risk of death only in younger adults, while associations were attenuated after risk factor adjustment and became non-significant in older age groups. This highlights the importance of considering not only absolute but also relative scores (within age and sex strata) when interpreting CAC burden.[28] While in elderly individuals a CAC score of 1-10 represents a relatively low burden within the CAC score distribution for this age group[1,28] (e.g., below the 25$^{th}$ percentile of the CAC distribution for men ages 75-84 years of all four US racial/ethnic groups included in MESA[28]) the same score in a 35-year-old individual identifies a patient at increased risk of events compared to same age and sex peers. Our findings suggest that early, aggressive lifestyle interventions in adults <40 years of age with any detectable CAC may be highly beneficial. Detection of higher CAC burden (i.e., CAC>10) particularly at young adult ages should trigger the consideration of these and additional pharmacologic interventions even more strongly.

*Study Strengths*

Strengths of the present study include large sample size, long follow-up, and ascertainment of cause-specific mortality. These also allowed us to examine additional causes of death including stroke, heart failure, and pulmonary disease. An additional strength and novel contribution to the CAC=0 literature is the use of competing risk Fine and Gray modeling, which provides more accurate estimates of cause-specific risk in the presence of competing events.

*Study Limitations*

There are also several limitations to our study. First, this was a clinical population of asymptomatic patients referred for CAC scoring, as opposed to other non-selected cohorts such as MESA, which are composed ofvolunteers from the community. While this may reduce generalizability of our results to certain unselected populations, our study should be highly generalizable to patients commonly referred for CAC scoring in clinical practice. In addition, inclusion of a mostly White patient population in the CAC Consortium may limit generalizability of the present findings to other racial/ethnic groups.

Second, information on treatment initiation after CAC scoring was not available. While a limitation, subsequent treatment with pharmacotherapies such as statins would be generally expected to yield a conservative bias in the CHD/CVD analyses, as patients with CAC>0 would be more likely to be treated with those therapies, reducing their likelihood of developing incident CHD/CVD events and death.

Third, consistent with the changing epidemiology of CVD vs. cancer mortality,[29] there were likely cohort effects within our broad study period, with higher CVD death rates in patients enrolled earlier in our study. This likely explains, at least partly, why cumulative annual CHD and CVD mortality in CAC=0 drifted down with time over our study, while cancer mortality modestly rises.

Fourth, it is possible that some CAC=0 patients included in the CAC Consortium had been referred for CT assessment for other, non-coronary health concerns, their CAC score being assessed as part of the same exam. This would explain the counterintuitive, slightly higher death rates (particularly cancer death) observed in CAC=0 as compared to CAC 1-10 patients during the first year of follow-up. This would have yielded a conservative bias when comparing CAC=0 patients (which would be at increased risk of death) to those with minimal CAC.

Finally, there were likely some missed deaths in the CAC Consortium. Our prior analyses have suggested that mortality rates may be 15-30% higher than we report, due to limitations inherent in vital status ascertainment in the US.[16] However, this phenomenon should be non-differential across causes of death, which would be expected to bias the results towards the null. Moreover, even accounting for missed events, patients with CAC=0 would still have a highly favorable prognosis (<3 deaths per 1000 patient-years).

## Conclusions

In conclusion, we have shown that zero CAC, which is a frequent finding, is associated with stably low rates of CHD and CVD mortality over 12-year follow-up, with cancer as the predominant (twice as likely) cause among the infrequent deaths in these patients. Our results support the emerging consensus that CAC=0 represents a unique population with highly favorable all-cause prognosis, who may be considered for more flexible treatment goals in primary prevention. On the other hand, younger individuals <40 years with minimal CAC 1-10 are at increased risk, and should be considered a distinct risk group. At any age, a CAC score >10 is associated with a markedly increased risk of death from any cause compared to CAC=0 individuals, with CVD death more common than cancer death. Further research with even longer follow-up is needed to better understand the mechanisms underlying the “healthy aging” observed in CAC=0 patients, as well as their lifetime trajectory.


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## DISCLOSURES

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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## FIGURE LEGENDS

**Figure 1.** Incidence proportion of all-cause and cause-specific death events during follow-up, by baseline CAC score.

Results are presented in %.

Abbreviations: CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease

**Figure 2.** Distribution of causes of death by baseline CAC score.

Results are presented in %, among participants experiencing death during follow-up.

Abbreviations: CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease

**Figure 3.** Cumulative incidence rates of all-cause mortality during follow-up, by baseline CAC score.

Results are presented as cumulative incidence rates between baseline and up to each year of follow-up, per 1000 person-years. The X axis presents years of follow-up.

Abbreviations: CAC = coronary artery calcium

**Figure 4.** Cumulative incidence rates of CVD death and cancer death during follow-up, by baseline CAC score.

Results are presented as cumulative incidence rates between baseline and up to each year of follow-up, per 1000 person-years. The X axis presents years of follow-up.

Abbreviations: CAC = coronary artery calcium; CVD = cardiovascular disease

## TABLES

**Table 1.** Baseline characteristics of the study participants.

| | Total | CAC | | |
|---|---|---|---|---|
| | | =0 | 1-10 | >10 |
| | N=66,636 | N=29,757 | N=7,808 | N=29,071 |
| **Age** | 54.4 (10.6) | 49.9 (9.2) | 52.7 (9.3) | 59.5 (10.0) |
| **Women** | 22,003 (33.0) | 13,230 (44.5) | 2,153 (27.6) | 6,620 (22.8) |
| **Race (N=42,964)** | | | | |
| Non-Hispanic White | 38,277 (89.1) | 16,933 (88.7) | 4,308 (87.5) | 17,036 (89.9) |
| Asian | 1,621 (3.8) | 794 (4.2) | 181 (3.7) | 646 (3.4) |
| African-American | 977 (2.3) | 429 (2.3) | 140 (2.8) | 408 (2.2) |
| Hispanic | 1,349 (3.1) | 620 (3.3) | 188 (3.8) | 541 (2.9) |
| **Hypertension** | 20,625 (31.0) | 6,782 (22.8) | 2,291 (29.3) | 11,552 (39.7) |
| **Diabetes** | 4,503 (6.8) | 1,163 (3.9) | 464 (5.9) | 2,876 (9.9) |
| **Dyslipidemia** | 37,861 (56.8) | 15,112 (50.8) | 4,466 (57.2) | 18,283 (62.9) |
| **Current Smoking** | 6,400 (9.6) | 2,646 (8.9) | 718 (9.2) | 3,036 (10.4) |
| **Family History of CHD** | 30,721 (45.6) | 13,567 (45.6) | 3,719 (47.6) | 13,435 (46.2) |
| **Number of Risk Factors** | 1.5 (1.0) | 1.3 (1.0) | 1.5 (1.0) | 1.7 (1.0) |
| **10-Year ASCVD Risk*** | 4.4 (1.9, 9.2) | 2.4 (1.2, 4.7) | 4.0 (2.0, 7.5) | 7.9 (4.1, 14.8) |
| **ASCVD Risk* Categories** | | | | |
| <5% | 36,793 (55.2) | 22,882 (76.9) | 4,688 (60.0) | 9,223 (31.7) |

| | | | | |
|---|---|---|---|---|
| 5-7.5% | 8,939 (13.4) | 3,181 (10.7) | 1,163 (14.9) | 4,595 (15.8) |
| 7.5-20% | 15,665 (23.5) | 3,264 (11.0) | 1,679 (21.5) | 10,722 (36.9) |
| >20% | 5,239 (7.86) | 430 (1.45) | 278 (3.56) | 4,531 (15.6) |

* 10-Year ASCVD risk estimated using the American College of Cardiology / American Heart Association Pooled Cohort Equations

Categorical variables presented as number (percentage), and continuous variables presented as mean (standard deviation) or median (interquartile range). All P values for the comparison across CAC categories <0.001, except for family history of CHD (0.01)

Abbreviations: ASCVD = atherosclerotic cardiovascular disease risk; CAC = coronary artery calcium; CHD = coronary heart disease

**Table 2.** Associations between baseline CAC burden, all-cause and cause-specific mortality during follow-up.

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| **All-cause death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.39 (1.19, 1.62) | 1.13 (0.94, 1.38) | 1.04 (0.89, 1.22) |
| CAC>10 | 4.16 (3.80, 4.55) | 1.75 (1.54, 1.99) | 1.63 (1.48, 1.81) |
| **CVD death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.70 (1.23, 2.33) | 1.26 (0.84, 1.89) | 1.22 (0.88, 1.68) |
| CAC>10 | 6.79 (5.61, 8.23) | 2.65 (2.03, 3.45) | 2.31 (1.88, 2.85) |
| **CHD death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.47 (0.87, 2.46) | 0.87 (0.43, 1.79) | 1.00 (0.59, 1.68) |
| CAC>10 | 9.16 (6.86, 12.23) | 3.61 (2.39, 5.45) | 2.83 (2.07, 3.86) |
| **Cancer death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.11 (0.87, 1.41) | 0.83 (0.61, 1.13) | 0.88 (0.69, 1.12) |
| CAC>10 | 2.70 (2.36, 3.10) | 1.14 (0.94, 1.39) | 1.19 (1.02, 1.40) |

Results presented as hazard ratios from Cox proportional hazards regression analyses (all-cause death analyses), and subdistribution hazard ratios from Cox proportional hazards regression analyses accounting for competing risks (cause-specific death analyses)

Model 1 was unadjusted; Model 2 adjusted for age and sex; Model 3 further adjusted for hypertension, hyperlipidemia, family history of CHD, diabetes, and current smoking status.

Abbreviations: CVD = cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; Ref. = reference

**Table 3.** Associations between baseline CAC burden, all-cause and cause-specific mortality during follow-up, by sex.

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| ***Women (N=22,003)*** | | | |
| **All-cause death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.77 (1.39, 2.25) | 1.17 (0.92, 1.49) | 1.14 (0.90, 1.46) |
| CAC>10 | 4.77 (4.16, 5.48) | 1.94 (1.67, 2.25) | 1.80 (1.54, 2.10) |
| **CVD death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 2.24 (1.33, 3.80) | 1.36 (0.79, 2.33) | 1.30 (0.76, 2.21) |
| CAC>10 | 8.99 (6.63, 12.18) | 2.92 (2.10, 4.04) | 2.57 (1.87, 3.54) |
| **CHD death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.73 (0.70, 4.28) | 1.00 (0.39, 2.52) | 0.95 (0.38, 2.41) |
| CAC>10 | 9.66 (6.03, 15.47) | 2.80 (1.70, 4.64) | 2.46 (1.50, 4.05) |
| **Cancer death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.50 (1.05, 2.14) | 1.12 (0.78, 1.61) | 1.10 (0.77, 1.58) |
| CAC>10 | 2.82 (2.29, 3.47) | 1.42 (1.12, 1.80) | 1.36 (1.07, 1.73) |
| ***Men (N=44,633)*** | | | |
| **All-cause death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.30 (1.06, 1.56) | 1.30 (1.06, 1.56) | 0.95 (0.78, 1.17) |
| CAC>10 | 4.25 (3.76, 4.80) | 4.25 (3.76, 4.80) | 1.50 (1.31, 1.71) |
| **CVD death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.48 (0.99, 2.21) | 1.48 (0.99, 2.21) | 1.08 (0.72, 1.61) |
| CAC>10 | 6.1 (4.76, 7.82) | 6.1 (4.76, 7.82) | 2.02 (1.55, 2.63) |
| **CHD death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.34 (0.71, 2.53) | 1.34 (0.71, 2.53) | 0.98 (0.52, 1.84) |
| CAC>10 | 8.77 (6.04, 12.73) | 8.77 (6.04, 12.73) | 2.88 (1.94, 4.26) |
| **Cancer death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.01 (0.73, 1.41) | 1.01 (0.73, 1.41) | 0.76 (0.55, 1.06) |
| CAC>10 | 2.99 (2.48, 3.61) | 2.99 (2.48, 3.61) | 1.10 (0.89, 1.36) |

Results presented as hazard ratios from Cox proportional hazards regression analyses (all-cause death analyses), and subdistribution hazard ratios from Cox proportional hazards regression analyses accounting for competing risks (cause-specific death analyses)

Model 1 was unadjusted; Model 2 adjusted for age; Model 3 further adjusted for hypertension, hyperlipidemia, family history of CHD, diabetes, and current smoking status.

Abbreviations: CVD = cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; Ref. = reference

**Table 4.** Associations between baseline CAC burden, all-cause and cause-specific mortality during follow-up, by age strata.

| | <40 years (N=4,855) | 40-50 years (N=17,802) | 50-60 years (N=24,838) | 60-70 years (N=13,418) | ≥70 years (N=5,723) |
|---|---|---|---|---|---|
| **All-cause death** | | | | | |
| CAC=0 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| CAC 1-10 | 2.91 (1.41, 6.00) | 0.80 (0.52, 1.23) | 1.20 (0.92, 1.58) | 0.98 (0.74, 1.31) | 0.97 (0.68, 1.40) |
| CAC>10 | 2.90 (1.36, 6.21) | 1.81 (1.37, 2.38) | 1.77 (1.47, 2.13) | 1.43 (1.19, 1.72) | 1.80 (1.44, 2.25) |
| **CVD death** | | | | | |
| CAC=0 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| CAC 1-10 | 4.45 (1.34, 14.85) | 1.17 (0.56, 2.42) | 1.18 (0.59, 2.34) | 1.07 (0.57, 2.01) | 1.15 (0.59, 2.26) |
| CAC>10 | 3.88 (0.92, 16.37) | 1.87 (1.11, 3.16) | 3.17 (2.07, 4.86) | 2.11 (1.39, 3.19) | 2.33 (1.52, 3.56) |
| **CHD death** | | | | | |
| CAC=0 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| CAC 1-10 | 1.25 (0.14, 10.91) | 1.67 (0.57, 4.91) | 1.74 (0.66, 4.58) | 0.42 (0.12, 1.47) | 0.66 (0.21, 2.09) |
| CAC>10 | 4.12 (0.66, 25.85) | 2.97 (1.32, 6.69) | 5.08 (2.68, 9.63) | 1.89 (1.08, 3.31) | 2.43 (1.33, 4.46) |
| **Cancer death** | | | | | |
| CAC=0 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) |
| CAC 1-10 | - | 0.76 (0.34, | 0.91 (0.62, | 0.88 (0.58, | 0.78 (0.42, |

| | | | | | |
|---|---|---|---|---|---|
| | | 1.70) | 1.35) | 1.34) | 1.45) |
| CAC>10 | 1.64 (0.14, 19.00) | 1.34 (0.79, 2.23) | 1.08 (0.82, 1.41) | 1.07 (0.82, 1.40) | 1.23 (0.84, 1.78) |

Results presented as hazard ratios from Cox proportional hazards regression analyses (all-cause death analyses), and subdistribution hazard ratios from Cox proportional hazards regression analyses accounting for competing risks (cause-specific death analyses)

All analyses adjusted for sex, hypertension, hyperlipidemia, family history of CHD, diabetes, and current smoking status.

Abbreviations: CVD = cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; Ref. = reference

**FIGURES**

**Figure 1.** Incidence proportion of all-cause and cause-specific death events during follow-up, by baseline CAC score.

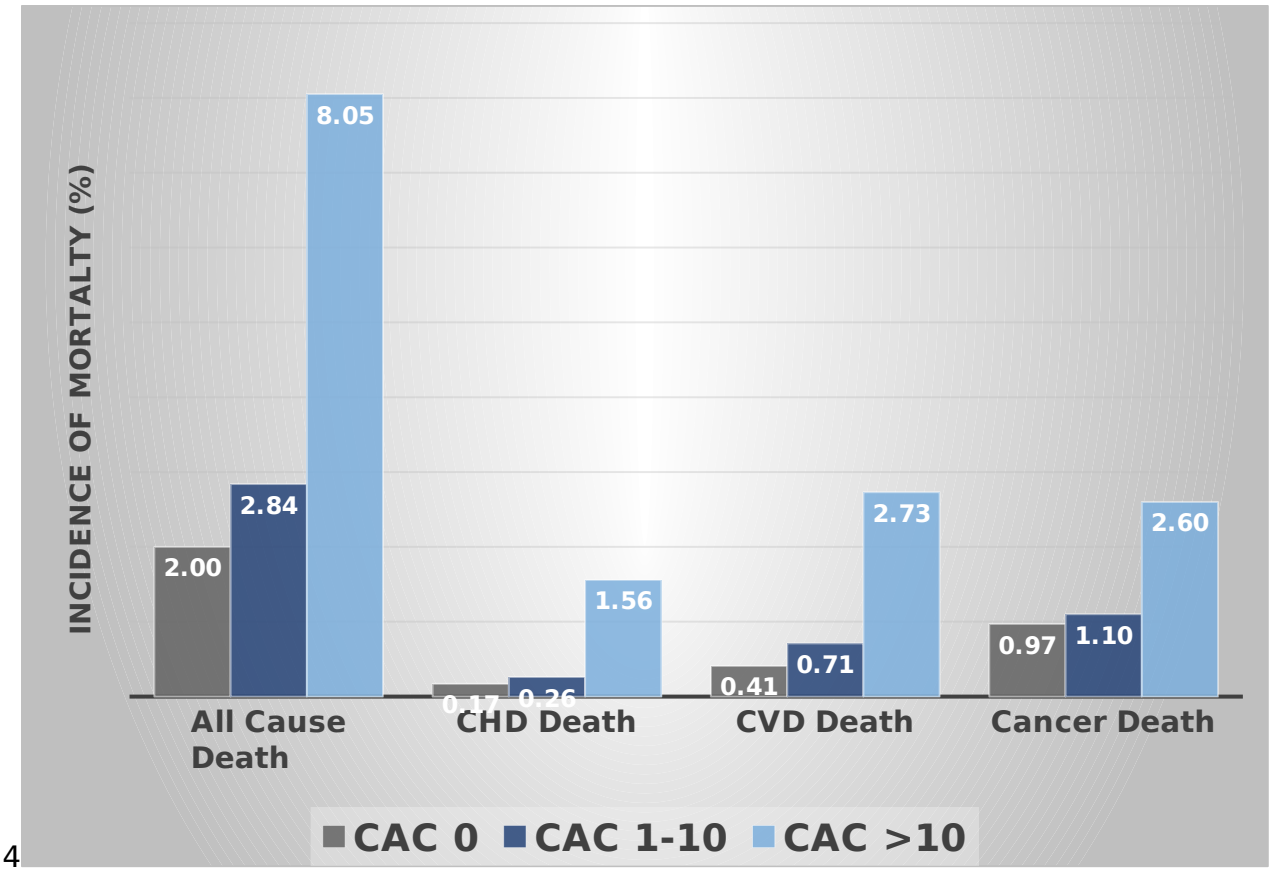


**Figure 2.** Distribution of causes of death among participants dying during follow-up, by baseline CAC score.

*Figure 2A. Baseline CAC=0*

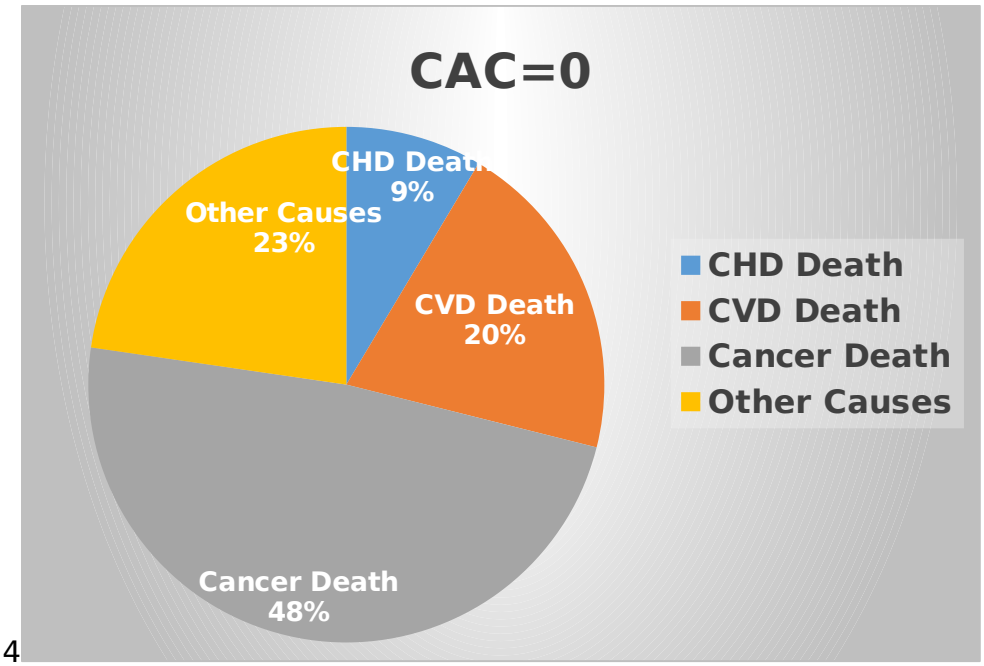



*Figure 2B. Baseline CAC 1-10*

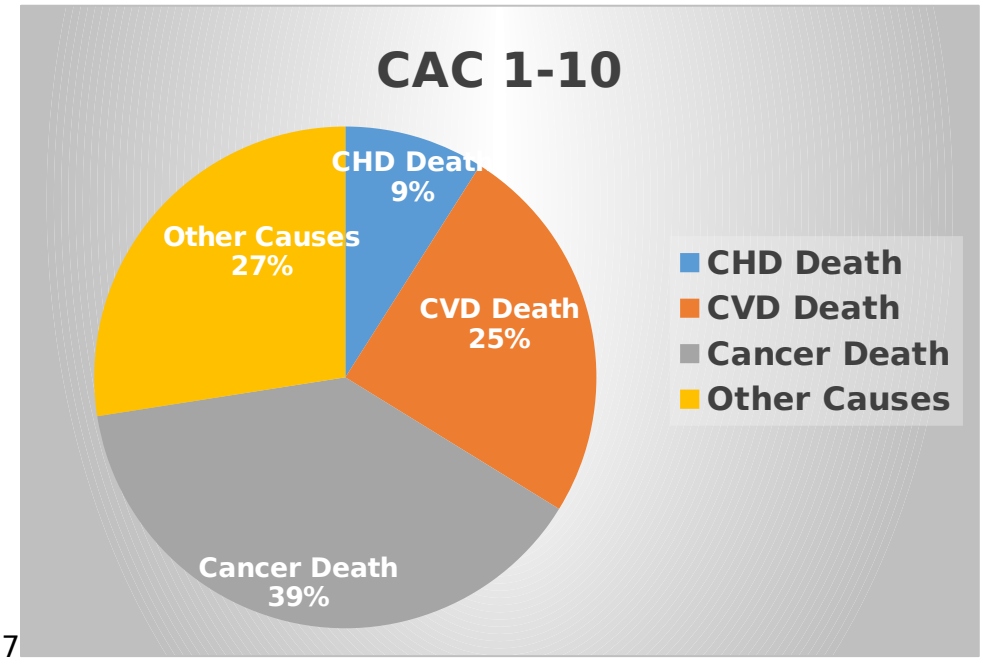


*Figure 2C. Baseline CAC>10*

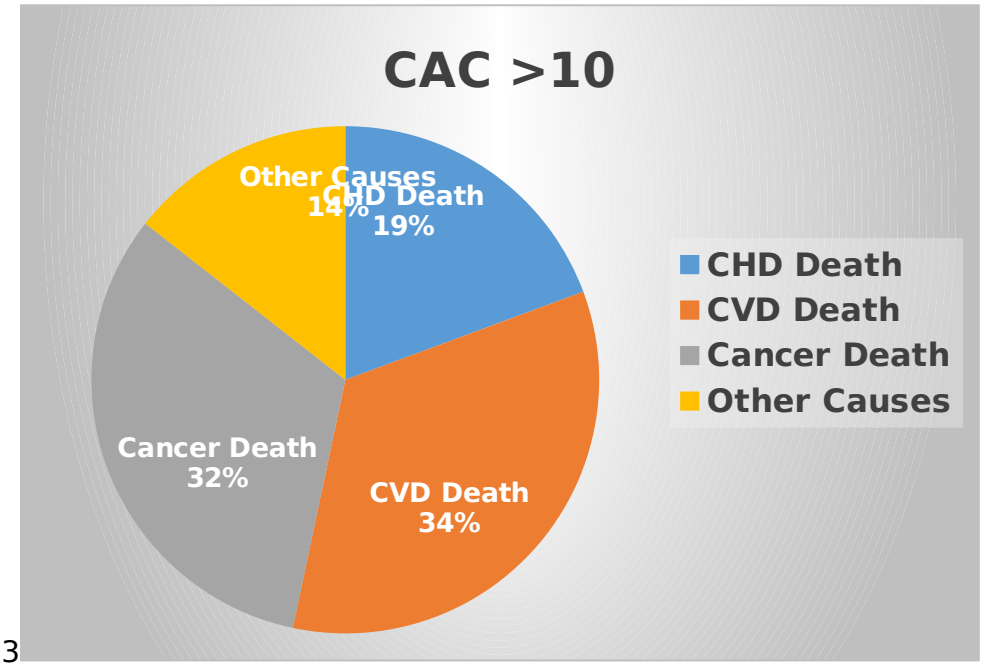


**Figure 3.** Cumulative incidence rates of all-cause mortality during follow-up, by baseline CAC score.

*Figure 3A. Cumulative incidence rates of all-cause mortality for CAC=0, CAC 1-10 and CAC >10.*

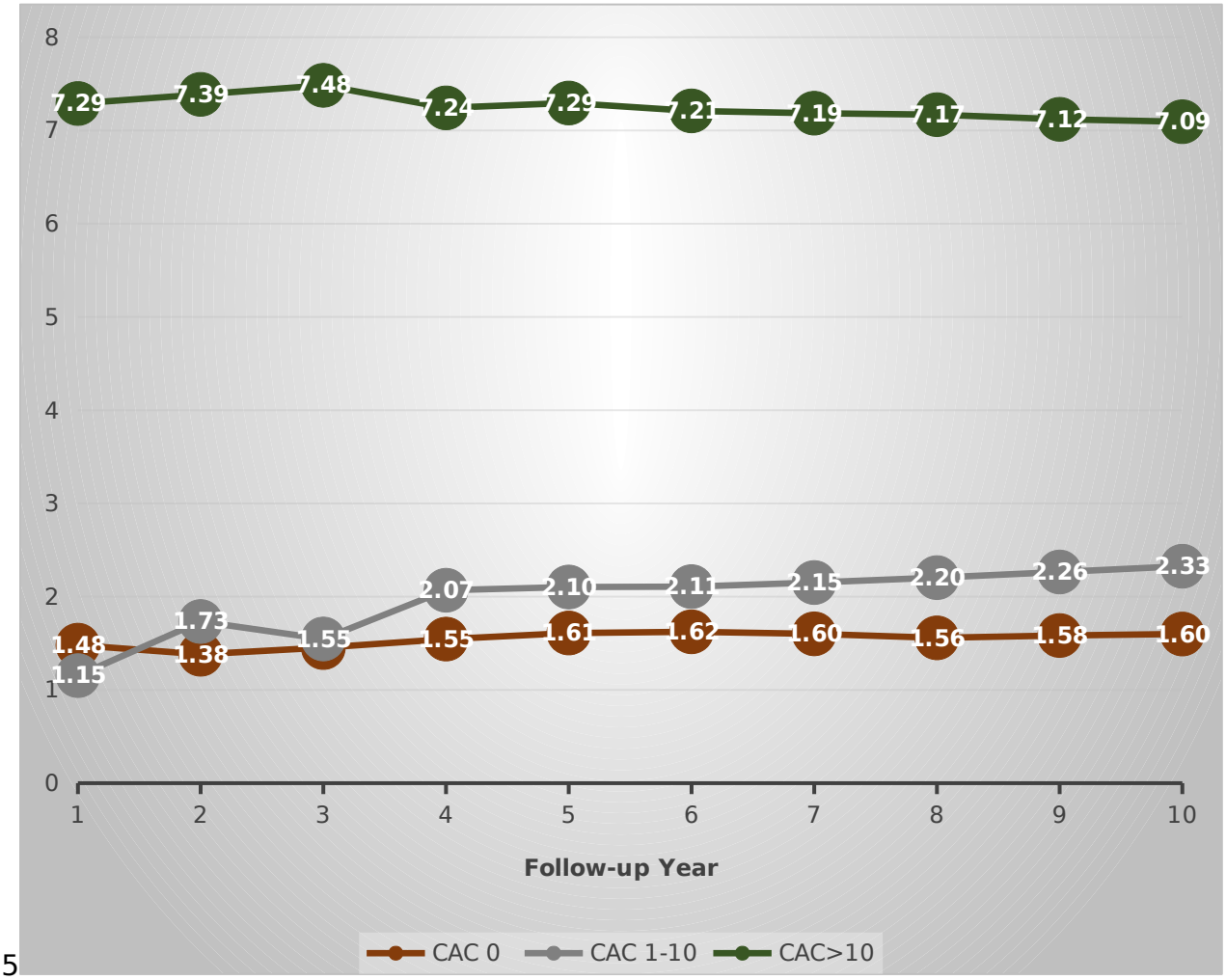


*Figure 3B. Cumulative incidence rates of all-cause mortality for CAC=0 and CAC 1-10 using an alternative Y axis scale.*

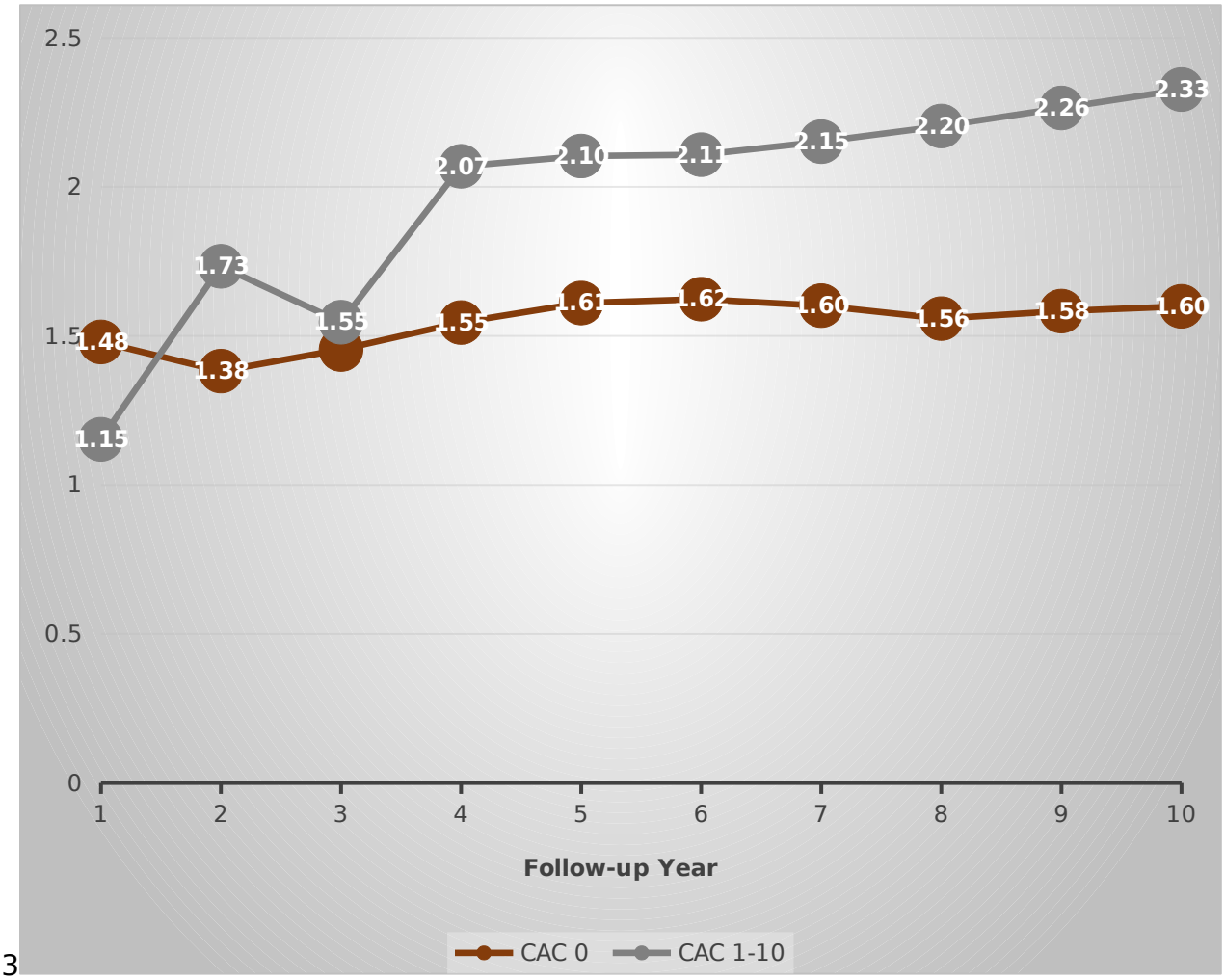
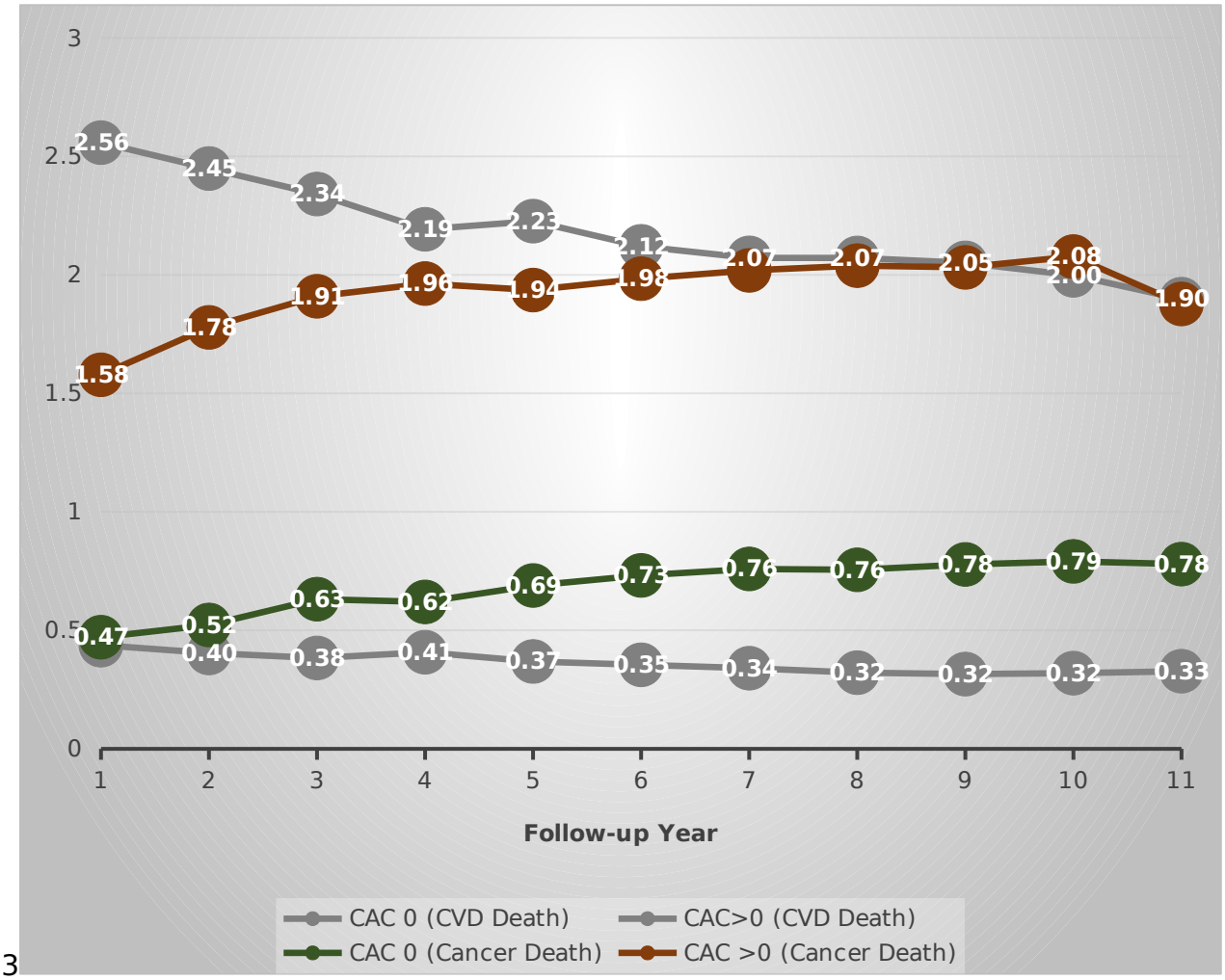


**Figure 4.** Cumulative incidence rates of CVD death and cancer death during follow-up, by baseline CAC score.



# Supplementary Appendix

## SUPPLEMENTARY METHODS

*Risk Factor Definitions in the CAC Consortium*

Hypertension was considered present if there was a prior diagnosis of hypertension or treatment with anti-hypertensive therapy. Blood pressure taken at the time of CT scanning was not used to override diagnoses of hypertension.

Dyslipidemia was defined as a prior diagnosis of primary hyperlipidemia (LDL-C >160 mg/dL), prior diagnosis of dyslipidemia (elevated triglycerides >150 mg/dL and/or low HDL-C <40 mg/dL in men and <50 mg/dL in women), or treatment with any lipid-lowering drug.

For the present analysis, current smoking status was considered present or absent.

Diabetes was defined as a prior diagnosis of diabetes or treatment with oral hypoglycemic drugs or insulin.

Family history of CHD was predominantly determined by the presence of a first degree relative with a history of CHD, however one site (11% of patients) used a definition of premature family history (<55 years in old in a male relative and <65 years old in a female relative).

**SUPPLEMENTARY TABLES**

**Supplementary Table S1.** Associations between baseline CAC burden and other causes of death.

| | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| **Stroke death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.94 (0.94, 4.03) | 1.52 (0.73, 3.18) | 1.51 (0.72, 3.16) |
| CAC>10 | 6.22 (3.92, 9.86) | 2.42 (1.45, 4.03) | 2.30 (1.38, 3.83) |
| **Heart failure death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 8.61 (2.23, 33.25) | 6.07 (1.51, 24.38) | 5.89 (1.49, 23.39) |
| CAC>10 | 13.91 (4.31, 44.91) | 4.45 (1.23, 16.18) | 3.91 (1.09, 13.98) |
| **Other circulatory death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.38 (0.79, 2.40) | 1.09 (0.62, 1.92) | 1.07 (0.61, 1.88) |
| CAC>10 | 3.85 (2.78, 5.33) | 1.75 (1.22, 2.52) | 1.62 (1.12, 2.33) |
| **Non-CVD death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 1.31 (1.10, 1.57) | 1.03 (0.86, 1.23) | 1.03 (0.86, 1.23) |
| CAC>10 | 3.40 (3.07, 3.77) | 1.52 (1.36, 1.71) | 1.46 (1.30, 1.64) |
| **Pulmonary death** | | | |
| CAC=0 (Ref.) | 1.00 | 1.00 | 1.00 |
| CAC 1-10 | 3.24 (1.58, 6.65) | 2.22 (1.08, 4.59) | 2.22 (1.08, 4.59) |
| CAC>10 | 9.11 (5.43, 15.29) | 2.66 (1.53, 4.61) | 2.46 (1.41, 4.28) |

Results presented as subdistribution hazard ratios from Cox proportional hazards regression analyses accounting for competing risks.

Model 1 was unadjusted; Model 2 adjusted for age and sex; Model 3 further adjusted for hypertension, hyperlipidemia, family history of CHD, diabetes, and current smoking status.

1Abbreviations: CVD = cardiovascular disease; CAC = coronary artery

2calcium; CHD = coronary heart disease; Ref. = reference

3